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SILVER SALVARSAN IN THE TREATMENT OF SYPHILIS.*

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THROUGH the courtesy of Ehrlich's distinguished pupil and successor, Professor Kolle, early in November, 1919, Colonel Earl H. Bruns, chief surgeon, A. F. in G., received 1000 ampoules of silver salvarsan from the George Speyer Haus Laboratories, Frankfurt, Germany. Colonel Bruns turned this preparation over to Major Robert W. Kerr, Medical Corps, the Commanding Officer of the Base Hospital (now Station Hospital), A. F. in G., Coblenz, Germany, with instructions concerning its use which he had obtained personally from Professor Kolle. The first results seemed favorable and its further use was decided upon. Additional

* Weichbrodt, Knauer, Seoli-Bonn and Gennerich: *Ztschr. f. Aerztliche Fortbildung*, Georg Speyer Haus, Frankfurt.

supplies of this preparation were obtained through medical department procurement.

Since that time over 800 patients have been treated with silver salvarsan and mercury, more than 6000 injections having been given at the Base Hospital and Convalescent Hospital by or under the direction of the following officers: Majors Carter and Flynn; Captains Kimbrough, Raycroft and Moore; Lieutenants Cowen, Thomas, Blackburn, Bourbon and myself. The laboratory work in connection with the Venereal Clinic has been done by Major Gentzkow, Lieutenant McNeil and Lieutenant Elmendorf.

Composition and Description of Silver Salvarsan. Kolle¹ states that silver salvarsan contains 22.4 per cent. arsenic and 14.1 per cent. silver. Bauer² says that the silver in silver salvarsan is not present in the oxide or colloid form, but in a complex combination that may be considered half colloids, on the boundary between colloids and crystalloids.

He advances the theory, based on different experiments, that these semicolloids act as colloids in the system. He states that in silver salvarsan, neosalvarsan and old salvarsan the relative chemotherapeutic coefficient is silver salvarsan 1 to 25, neosalvarsan 1 to 10, old salvarsan 1 to 10. He further states that the arsenic component is materially decreased in silver salvarsan owing to the combination with the antisyphilitic silver component. His diffusion experiments make it seem probable that silver salvarsan is hydrolized in the body and set free as true colloids. A single dose of two-tenths (0.2) gm. of silver salvarsan contains 0.0254 silver and 0.043 of arsenic.

Silver salvarsan is prepared in the Ehrlich Laboratories at Frankfurt and the powder is placed in ampoules in the following doses: One-tenth (0.1) gm., fifteen hundredths (0.15) gm., two-tenths (0.2) gm., three-tenths (0.3) gm. The powder is grayish black and in solution takes on an ichthyol brown color.

Characteristics of Spoiled Silver Salvarsan. Silver salvarsan in the original ampoules keeps for an unlimited time so long as it is not damaged. Small cracks in the glass permitting the entrance of air cause silver salvarsan to become decomposed and thereby made poisonous. The decomposition is not so easily discernible in looking at an ampoule of the silver salvarsan while in powder form as when placed in a solution.

If the silver salvarsan has deteriorated the powder is darker in color and does not change to an ichthyol brown color when placed in solution, but takes on an opalescence of pronounced cloudiness, or it floats around on the surface of the water in black particles in which the undissolved silver salvarsan is recognized by the naked eye when the solution is held to the light.

Silver Salvarsan as a Spirocheticide. Kolle and Ritz³ state that silver salvarsan is to be considered a true combined preparation

containing two chemotherapeutically effective components, silver having a catalytic effect on the salvarsan molecule. They further state that it has been experimentally proved that arsenobenzol is a direct spirocheticide, because of anchoring of the arsenic in the spirochetic plasma. Many experiments, especially those showing the slow disappearance of the spirochetæ after the administration of this drug, incline to the opinion that silver acts as a restricting agent on the multiplication of spirochetæ. The action of the silver in silver salvarsan is successful in preventing an increase of spirochetæ because of the specific affinity of the salvarsan to the spirochetæ, the silver with the whole molecule of the silver salvarsan is anchored fast to the spirochetæ of the syphilitic tissues. For this reason the combination of the silver with the salvarsan is of special chemical therapeutic value. The silver salvarsan acts also on the spirochetæ within the syphilitic tissue as a combination remedy in the sense that this term was used by Ehrlich.

In a series of experiments they have shown that in rabbits the curative dose of the metal silver, or its salts, is one-hundredth (0.01) gm. to two-hundredths (0.02) gm. per kilogram of the rabbit's weight, the toxic dose for rabbits being six-hundredths (0.06) gm. to seven-hundredths (0.07) gm. The spirochetæ disappear slowly but surely from the infected rabbit. The hard chancre softens and finally disappears. Not only does colloidal silver but also organic and inorganic silver salts combined with albumin influence the manifestation of syphilis and the spirochetæ. The effect on the spirochetæ and its manifestations is slower with all silver salts than with arsenobenzol, but the former can be given in larger doses with less toxic effect. Spirochetæ disappear more slowly with colloidal silver than with non-colloidal compounds. The primary manifestations of syphilis in experimental animals disappear in from three to five weeks after therapeutic healing doses of silver compounds. Animal experimentation finds silver salvarsan twice as effective as salvarsan (606) and three times as effective as neosalvarsan (914). Kolle further states that silver salvarsan is old salvarsan in active form plus silver and that 0.25 silver salvarsan equals 0.4 old salvarsan.

Technic of Administration of Silver Salvarsan. Bruhns and Lowenberg⁴ use one-tenth (0.1) gm. of silver salvarsan dissolved in 20 c.c. of freshly distilled sterilized water; in the larger doses 30 to 40 c.c. of freshly distilled sterilized water.

Kerl⁵ uses 6 c.c. of freshly distilled water to every one-tenth (0.1) gm. of silver salvarsan. Delbanco and Zimmern⁶ make a solution with from 10 to 20 c.c. according to quantity of preparation. Lenzmann⁷ uses 20 to 40 c.c.; four-tenths (0.4) per cent. solution of sodium chloride. Schoenfeld and Birnbaum⁸ prefer 60 to 80 c.c. of normal sodium chloride (C. P.) solution. Kolle¹ recom-

mends 10 c.c. of distilled water to each one-tenth (0.1) gm. Dreyfus⁹ states that we should use only redistilled sterilized water from the Jena glass apparatus, avoiding the use of any metal that would come in contact with the solution except the platinum needle.

Kerl⁵ prefers a modified Arzt Schramek syringe. Lenzmann⁷ uses a Lieberg syringe. Birnbaum⁸ uses the Schreibus glass syringe. Kolle¹ suggests Wechselmann's apparatus.

Practically all the above-mentioned authorities emphasize the importance of giving the solution very slowly. Bruhns and Lowenberg⁴ state that the least time required for each injection should be at least two minutes. Kolle¹ calls particular attention to the irritating effect of silver salvarsan on the tissues and states that caution should be used so that injury to the inner wall of the vein does not occur and that great care is used in seeing that the needle is in the vein properly before administering the solution.

The technic used at the Station Hospital and Convalescent Hospital is as follows:

The water is distilled the day previous to its use. The distilled water is boiled on the day of the administration of the silver salvarsan. The water used is at room temperature. The silver salvarsan ampoules are immersed in 95 per cent. of alcohol, 20 c.c. of the sterilized distilled water are placed in a 60 c.c. medicine glass and the contents of the ampoule containing the silver salvarsan are dropped into the glass containing the distilled water. The silver salvarsan powder floats around on the surface of the water until it is completely dissolved, which takes approximately one minute. The solution now takes on an ichthyol brown color. The contents of the medicine glass are now drawn up into a 30 c.c. Luer syringe. Just prior to the insertion of the needle the operator dries same with a piece of sterile gauze in order to prevent the solution from coming into contact with the tissues. After the needle is introduced into the vein enough blood is withdrawn to fill the syringe. By this means we are positive of the needle being in the lumen of the vein, and, according to Kolle, the toxicity of silver salvarsan is immediately reduced by the addition of albumin or serum. The injection of the solution is made slowly, requiring approximately one minute. The needle is withdrawn quickly and the operator raises the patient's arm and uses marked pressure at the site of the injection in order to prevent extravasation of the fluid back into the tissues.

Dosage. Galewsky¹¹ considers small doses of silver salvarsan necessary in the treatment of syphilis. He commences it with five-hundredths (0.05) gm. for anemic women, otherwise one-tenth (0.1) gm.; increases the dose every four or five days to a final maximum dose of three-tenths (0.3) gm. to men and twenty-five-hundredths (0.25) gm. for women. Total given by him to

men in the course of treatment is 1.8 gm. and for women 1.5 gm. He ordinarily gives eight to fifteen injections of silver salvarsan in the first course of treatment for primary seronegative syphilis and four to six injections in after-treatment. In order to avoid what he terms spirochetæ fever in virulent secondary stage of syphilis, he gives a first dose of five-hundredths (0.05) gm. and second dose of fifteen-hundredths (0.15) gm.

Dreyfus⁹ states that no fixed total dose has been found as yet. He has given as high as 3 or 4 gms. to a patient in from six to ten weeks without after-effects.

Schoenfeld and Birnbaum⁸ state that they use for the first two or three doses for men one-tenth (0.1) to two-tenths (0.2) gm., and for women one-tenth (0.1) gm. to fifteen-hundredths (0.15) gm. For the next five or six doses in strong men they give three-tenths (0.3) gm. to thirty-five hundredths (0.35) gm. and for strong women two-tenths (0.2) gm. to twenty-five-hundredths (0.25) gm. They follow this treatment with three or four doses at six-day intervals, giving men twenty-five-hundredths (0.25) gm. and women two-tenths (0.2) gm. They state that the average total dose of 2.5 to 2.75 gm. for men and 2 gm. to 2.5 gm. for women should be given in ten to twelve injections.

Bruhns and Lowenberg⁴ give the following course of treatment: Twelve injections of silver salvarsan with three or four days' interval. For the first dose they give one-tenth (0.1) gm. followed by five doses of two-tenths (0.2) gm. and this is followed by six doses of twenty-five-hundredths (0.25) gm.

Kerl⁵ administers one-tenth (0.1) gm. and two-tenths (0.2) gm. of silver salvarsan on two succeeding days, and after an eight-day interval repeats the treatment until he obtains a negative Wassermann reaction. Later, because of the slow response of Wassermann reaction, he gave one-tenth (0.1) gm., two-tenths (0.2) gm.; two-tenths (0.2) gm. on three successive days and repeated after an eight-day interval.

Delbanco and Zimmern⁶ give on first dose five-hundredths (0.05) gm. or one-tenth (0.1) gm. Second dose, one-tenth (0.1) gm. and the next six to ten injections a dosage of two-tenths (0.2) gm. or twenty-five hundredths (0.25) gm. They gave their injections with an interval of from three to five days. They state that silver salvarsan may be given daily without bad results. Boas and Kissmeyer¹² gave only four injections in each treatment with a dosage of fifteen-hundredths (0.15) gm., twenty-hundredths (0.20) gm., and twenty-five-hundredths (0.25) gm. They state that when treatment has been going on for some time there should be a long interval between each dose, at least as much as eight or ten days.

Lenzmann⁷ gives at the first dose one-tenth (0.1) gm., and if no bad effects follow he then gives fifteen-hundredths (0.15) gm. on

the third day, on the sixth day two-tenths (0.2) gm., ninth day twenty-five-hundredths (0.25) gm., then four injections of twenty-five-hundredths (0.25) gm. a week apart, and on the following week a dose of three-tenths (0.3) gm. He further states in seronegative primary syphilis five to six injections are sufficient, while in seropositive primary syphilis it requires seven to ten injections, according to the duration of the positive reaction. He states that fresh secondary syphilis up to two or two and a half months' duration requires only one treatment of ten to twelve injections if the serum reaction turns negative four weeks after taking up treatment. Where this was not the case the patient with secondary syphilis received a second treatment six weeks after the first, consisting of eight to ten injections at five-day intervals.

Rille and Frühwald¹³ give in single doses from two-tenths (0.2) gm. to four-tenths (0.4) gm. of silver salvarsan at intervals of from three to seven days, giving in all six to eight injections.

Kolle¹⁴ states that we must try to make the therapy so effective in the nine to eighteen injections, intervals from two to five days, that in perhaps 90 per cent. or more of the primary or early secondary cases we may expect complete sterilization. He advises beginning the treatment with one or two injections of one-tenth (0.1) gm. and increasing the dosage to two-tenths (0.2) gm. for women, with twenty-five-hundredths (0.25) gm. for men as a maximum dose, with an interval of four days. He says that we should never give more than 2 gm. of silver salvarsan in a month.

Major Kerr appointed a Board of Medical Officers consisting of Major H. P. Carter, Captains Kimbrough and Raycroft to investigate and recommend a treatment for the cure of syphilis with silver salvarsan. This Board recommended the following treatment:

An interval of seven days between each dose in each course of treatment.

Treatment to consist of four courses of silver salvarsan and gray oil.

In the first course of treatment the first dose to be fifteen-hundredths (0.15) gm. of silver salvarsan.

Second dose to be two-tenths (0.2) gm. of silver salvarsan.

And each of the remaining five doses of the first course to be three-tenths (0.3) gm. of silver salvarsan.

At the end of the first course of treatment a Wassermann blood test and then thirty days' rest.

In the second course of treatment three-tenths (0.3) gm. silver salvarsan for each dose, with seven-day intervals, then two and a half months' rest. Course to consist of seven doses.

The third course same as the second with ninety days' rest.

The fourth course same as second or third course.

In conjunction with and at the same time of each injection of

silver salvarsan give eight-hundredths (0.08) gm. gray oil, intramuscularly.

A Wassermann blood test was recommended after each course and a spinal fluid examination after the second course. During the second year of the disease perform every three months a Wassermann blood test and lumbar puncture with a complete serological examination of the spinal fluid. If at any time the Wassermann becomes positive treatment will be renewed. If at the end of the twenty-fourth month the Wassermann blood test and spinal fluid are negative the case is considered cured. This treatment was later somewhat modified by making an interval of four days between injections during the first course.

Primary Syphilis. Hoffman¹⁵ states that with one complete intensive course of treatment with mercury and salvarsan in primary syphilis we get a complete cure. Hoffmann, Neisser and Scholz¹⁵ claim a successful abortive cure of syphilis should be attained in from 80 to 100 per cent. of all cases, *provided the patient presents himself for treatment in the prepositive Wassermann period.* Fabry¹⁶ states that it is generally admitted now that in primary lues sterilization is obtained prior to the positive Wassermann period in 100 per cent. of all cases. Galewsky¹⁵ says that in all cases of early syphilis showing a positive dark field and negative Wassermann they continued to show a negative Wassermann throughout their treatment with silver salvarsan and during one year of observation following this.

It is believed we have reached the point where we should differentiate between primary and secondary syphilis by the Wassermann, and consider syphilis with primary lesions, primary syphilis, until Wassermann is positive, and then call it secondary syphilis. One should be extremely cautious in stating that a cure has been attained in any stage of syphilis, and observation of a patient, both from a clinical and serological standpoint, for a period of many years, appears to be essential before drawing any definite conclusion. To tell a patient that even in early syphilis he will be cured may give him a false security that in the end may do him an injustice as well as others. It would seem a better plan to tell the patient that some authors claim a cure, but that a cure is not at all certain. However, this much is certain, as a rule, syphilis, like tuberculosis, can be controlled if the patient follows instructions.

In a study of our syphilitic registers there were found 133 early cases where a diagnosis was made by a dark-field examination. These cases were divided into periods of from one to five, five to ten, ten to fifteen, fifteen to twenty, twenty to twenty-five, twenty-five to thirty and over thirty days, in which, according to patient's statement, he had noticed the primary lesion. The cases in question have been under treatment anywhere from four to ten months.

The following table shows those cases which have always had a negative Wassermann and those which at some time during treatment the Wassermann became plus minus, plus or double plus:

No. of cases.	Days lesion existed.	Always negative.	Became plus minus, single plus or double plus while under treatment.	Approximate percentage always negative.	Approximate percentage run plus minus, single plus or double plus.
27 . .	1 to 5	22	5	81	18
43 . .	6 to 10	29	14	63	32
17 . .	11 to 15	13	4	76	23
7 . .	16 to 20	3	4	42	57
6 . .	21 to 25	4	2	66	33
8 . .	25 to 30	3	5	34	62
25 . .	over 30	9	16	36	64
133		83	50	62	37

In the above small number of tabulated cases, all of which were diagnosed by a dark-field examination, 83 ran a negative Wassermann throughout their treatment, and 50 cases became plus minus, single plus or double plus during treatment. *In all the cases in this series which gave other than a negative Wassermann, such result was obtained a few days after beginning treatment, and this would lead one to believe that the case when starting treatment was on the verge of, or actually in, the secondary stage.* It must also be understood that the information regarding the time the primary lesion had been observed was necessarily obtained from the patient, many of whom stated that the lesion was about the size of a lead pencil when first noticed. Sometimes the information given by the patient was *not dependable* because his statement might be what he deemed best for his individual interest, having in mind the disciplinary action necessary by existing orders in case he failed to take the prophylactic treatment required at the time of exposure. Upon questioning many of these patients about the duration of the primary lesion, explaining the reason such information was desired and assuring them the truth would not lead to disciplinary measures, I found in many cases the soldier had noticed the primary lesion much longer than stated in his original questionnaire. Unfortunately, at the time the re-investigation was made with reference to the duration of the local lesion, in most of the cases where the table shows a primary lesion existed anywhere between one and twenty days and Wassermann became plus minus, plus or double plus, the soldier had left the American forces in Germany.

It is held that if the period of the *primary lesion* could be definitely stated in the above tabulated cases, where the lesion existed less than fifteen days they would always run a negative Wassermann. It will be of interest to follow this series of cases many years in order to determine if there has been an apparent abortive cure of

syphilis. Certainly in this type of case only can we expect an abortive cure.

Wassermann Reaction in Secondary Syphilis. Hahn¹⁷ states that in cases of seropositive lues he usually obtains a provisionally permanent negative Wassermann with ten injections of silver salvarsan. In such cases he gives two injections a week, one of two-tenths (0.2) gm. and one of three-tenths (0.3) gm. Galewsky¹⁵ says that in a great number of cases of positive Wassermanns after an injection of silver salvarsan the Wassermann remained negative and no symptoms showed up later. However, in these cases too short a time had elapsed to speak of permanent results. He also states there were isolated cases in which notwithstanding an application of salvarsan and mercury the Wassermann remained permanently positive. Sellei¹⁸ states that it is impossible to arrive at a definite conclusion from a survey of the cases so far treated with reference to the Wassermann. In two cases of secondary syphilis a reversion of the positive Wassermann was obtained within two or three weeks; however, he had a great number of cases where the Wassermann did not become negative until five or six weeks had passed. Hahn¹⁹ states that after twelve injections of silver salvarsan the Wassermann was always negative in fresh cases, and nearly always negative in older cases. In those cases in which it was not negative six more injections of silver salvarsan were made without injury to the patient, and in some instances he went beyond that number, reaching twenty-four injections. Fabry¹⁶ states that the reversion of the Wassermann in several cases had not come up to his expectations. In one-half of the cases treated by Hoffmann¹⁵ with ten injections of silver salvarsan the Wassermann reaction remained positive. Kolle¹ is of the opinion that we should obtain a negative Wassermann after twelve injections given as outlined by him under "Dosage" in this article, except in those isolated cases where there appeared to be a Wassermann-fast blood.

Knopf and Sinn,²⁰ in a series of 30 cases, 14 of which were treated with silver salvarsan alone and 16 with silver salvarsan and mercury, obtained the following results:

THE WASSERMANN BECAME NEGATIVE.

Without Hg, after silver salvarsan, gm.	Cases.	With Hg, after silver salvarsan, gm.	Cases.
0.8	1	0.8	7
1.2	3	1.2	4
1.6	6	1.6	1
1.8	2	2.4	1

The Wassermann remained positive twice without mercury and three times with mercury.

Müller³⁷ obtained the following serologic results in a series of 73 cases, using silver salvarsan alone:

Blood Wassermann after silver salvarsan.	L.I. 27	L.II. Manifest 27	L.II. Latent 13	L.III. 5	L. Hereditary 1
0.6	8	4	4	1	—
0.9	5	2	—	—	—
1.2	6	7	5	—	—
1.5	5	4	—	1	—
1.8	3	3	2	—	—
2.4	—	6	1	—	—
Total	27	26	13	2	0
Remained plus, p. c.	0	1	0	3	1

At the Station Hospital and Convalescent Hospital in a series of 61 cases of secondary syphilis manifested by a double plus Wassermann and clinical evidence of the disease in the secondary stage, the following negative Wassermann reactions were obtained after each dose of the first or second course of treatment:

FIRST COURSE OF TREATMENT.

No. of cases.	Doses of silver salvarsan.	Doses of ново-арсено- бензол.	Doses of gray oil.	Gave a negative Wassermann.
2	1	—	1	2
2	2	—	2	2
6	3	—	3	6
9	4	—	4	9
11	5	—	5	11
7	6	—	6	7
10	7	—	7	10
1	1	6	7	1
2	1	6	7	2
50				50

SECOND COURSE OF TREATMENT.

3	1	—	1	3
2	2	—	2	2
1	4	—	4	1
2	6	—	6	2
1	—	4	4	1
1	—	5	5	1
1	—	6	6	1
11				11

Our present schedule of treatment provides a rest of one month between first and second course of treatment. A summary relative to Wassermanns in this series of 61 cases may be tabulated as follows: 55 cases received silver salvarsan and gray oil of mercury; 47 of these cases gave a negative Wassermann in the first course, which consisted of seven treatments. The remainder (8 cases) gave a negative Wassermann in second course of seven treatments.

Approximately 83 per cent. gave a negative Wassermann at end of first course, and the remaining 17 per cent. gave a negative Wassermann at the end of second course. Six cases received sometime during their treatment silver salvarsan, novo-arseno-benzol, and gray oil of mercury, three gave a negative Wassermann in first course of treatment and three gave a negative Wassermann in second course of treatment. The number of cases in this series is, of course, too small for any final conclusions; however, it would appear that silver salvarsan has a slight advantage over novo-arseno-benzol relative to reversing the Wassermann.

Our syphilitic registers show 516 patients have completed the first, second or third course of treatment, approximately 70 per cent. of these cases gave a negative Wassermann after first course of treatment, 25 per cent. gave a negative Wassermann after second course of treatment and 5 per cent. gave a negative Wassermann after third course of treatment. In other words the selected cases in a series of 61 with manifestations of secondary syphilis give a higher percentage of negative Wassermanns than these 516 cases. This may possibly be explained by the fact that in our series of 516 cases there are many who received a portion of their treatment with novo-arseno-benzol, others did not take treatment regularly, and still others probably had a latent secondary or tertiary syphilis.

Silver Salvarsan with or without Mercury. Galewsky¹¹ states that a Wassermann is negative sooner with silver salvarsan than neo-salvarsan, he further prophesies that there will be no more relapses into premature tertiary or premature neurosyphilis. He considers silver salvarsan the best remedy discovered to date, and as a result of two years' experience he prefers straight silver salvarsan to the combination of mercury and salvarsan. He thinks there are fewer after-effects than in any other salvarsan preparation tried.

Bruhns and Lowenberg⁴ state that silver salvarsan often works quicker than mercury salvarsan combination.

Hauck²¹ believes that the addition of mercury is unnecessary in giving silver salvarsan, he says that owing to the toxic effect it paves the way to salvarsan poisoning.

Nolten²² states that mercury is superfluous when using silver salvarsan.

Gennerich²³ states that the addition of mercury is unnecessary in giving silver salvarsan. He further states that in seropositive and secondary lues the Wassermann turns negative somewhat sooner with silver salvarsan than with other salvarsan preparations, even in combination with mercury. He recommends mercury only in cases where a third treatment is necessary because of the long time since infection. He says it can be used between the silver salvarsan treatments because it prevents the spirochetæ from recuperating.

Fabry²⁴ states that one must be extremely careful with mercury and silver salvarsan in combination. He believes you should begin with silver salvarsan and not follow too closely with the mercury.

Von Notthaft²⁵ thinks that treatment with silver salvarsan and mercury at the same time is a mistake, owing to the toxic effect of mercury on the liver and kidneys. Weichselmann, Pinkus, Scholtz and von Notthaft have given up the use of mercury.

Boas and Kissmeyer¹² use mercury and silver salvarsan in combination. They state that mercury may be superfluous but it does no harm.

Lenz²⁶ states that he can only support in an approving manner the favorable results reported of silver salvarsan.

Kreibich²⁷ says that given the same proportion of arsenic, silver salvarsan is superior to old salvarsan, in which connection the inferior toxicity of the former permits a higher proportionate dosage.

Hahn¹⁷ states that the effect of silver salvarsan on syphilis is excellent; he has good results in all stages of syphilis. He had quite a number of patients who did not yield to other treatment but in whom after the administration of silver salvarsan the Wassermann became negative and remained so. He states that in sero-positive lues with an average of ten injections of silver salvarsan he was able to obtain a permanent negative Wassermann.

Goldberger²⁸ states that considering the inferior toxicity of silver salvarsan compared with old salvarsan, and its higher efficiency compared with neosalvarsan, it makes a valuable addition to antisyphilitic remedies. He thinks a combination with mercury appears to be the best treatment.

Sellei¹⁸ states that silver salvarsan operates in a very energetic manner and after a very short time the symptoms completely disappear. He believes the use of silver salvarsan particularly indicated where there is a nephritis present.

Clinical Effects of Silver Salvarsan and Mercury. Kreibich²⁷ states that the same rapid and intensive effect is obtained on the spirochetæ with silver salvarsan as with old salvarsan (606).

Galewsky¹¹ states that within twenty-four to twenty-eight hours after an injection of silver salvarsan the spirochetæ are often not to be found in the local lesion.

Bruhns and Lowenberg⁴ state that the exanthemata disappear remarkably quickly; the running papules dry up one day following the injection and soon heal.

Lenzmann⁷ states that there was a decided influence on the spirochetæ four hours after a dose of one-tenth (0.1) gm. of silver salvarsan, within twelve hours practically no living spirochetæ could be found.

Major Gentzkow and Lieutenant McNeil, in the Laboratory

Service at the Station Hospital, did not find living spirochetæ in the initial lesion twenty-four hours after an injection of silver salvarsan. Lieutenant Elmendorf, of the Convalescent Hospital, states that actively mobile spirochetæ have been found as long as twenty-one hours after an injection of silver salvarsan fifteen hundredths (0.15) gm. plus eight-hundredths (0.08) gr. of gray oil, and that inactive spirochetes were found in the local lesion as long as twenty-six hours after an injection of silver salvarsan and gray oil. The number of spirochetæ present in preparations made after an injection of silver salvarsan and gray oil were invariably greatly reduced. No organisms were found forty-eight hours after the time of injection of silver salvarsan.

The effect of silver salvarsan on all grades of syphilis is favorable. The local manifestations appear to clear up as rapidly as they did under the older salvarsan preparations. There is a decided change in the initial lesion after the first treatment, indurations pass off quickly, glands are reduced in size, exanthemata pale down and the mucous patches and condylomata heal rapidly. The best apparent results obtained by silver salvarsan, as in all cases of salvarsan preparations, were in those showing the ordinary clinical signs of secondary syphilis, with mucous patches in mouth and throat and exanthemata.

Immediate Effects Sometimes Seen after Silver Salvarsan. *Anaphylactoid Symptoms.* Swift (*Jour. Am. Med. Assn.*, 1912), after experimenting with guinea-pigs showed that a serum change took place after the first injection of salvarsan which led to the sensitizing of the animal.

J. Danepz, R.D.L. (*Academie de Science*, 1916) is of opinion that the after-effects of arsenobenzol compounds, alarming in many patients, are caused by a precipitation within the capillaries. According to him this precipitation is caused by the reaction of an antibody with the next injected arsenobenzol. He recommends giving oversensitive patients small preparatory doses.

Kolle, Schlossberger and Leupold,²⁹ in their experiments with mice showed that intravenous injections of small doses of salvarsan gave certain protection against an absolutely deadly dose twenty-four hours later. Many investigators place the after-effects of salvarsan preparations in the category of anaphylaxis, and insofar as the first injections are concerned, as parallel to primary serum poisoning. For this reason the after-effects manifested soon after the beginning of intravenous salvarsan injections are frequently called anaphylactoid.

Galewsky,¹⁵ speaking of so-called angioneurotocal symptoms, states that these symptoms were noticeable immediately after the first injection with some of the patients; with others they only became manifest after subsequent injections, so that it can only be a question of anaphylactoid manifestations after repeated intravenous injections of silver salvarsan. He states the symptoms

were chiefly noticeable in persons strongly alcoholic, or in patients suffering from heart affections.

Hahn¹⁹ says that the anaphylactoid symptom-complex turns up immediately after injection, he rarely came across it and it never became an embarrassing form except in the case of patients where an affection of the meninges was to be presumed.

Friedlaender³⁰ described cases suggesting to him the idea of anaphylaxis, wherein patients showed a few clonic twitches which were rapidly transformed into a shaking tremor of the whole body, cyanosis and weak pulse. In his opinion in these cases it is a question of Herxheimer reaction and the term anaphylaxis has only been used to account for the clinical similarity of the symptoms with genuine anaphylactoid manifestations.

From the most recent investigations by Schmalt, Giessen and Sachs³⁰ the presumption appears justified that anaphylaxis is not a chemical reaction of the albuminous substance but a process due to physical causes. These authors, apparently quite independently of one another, come to the same conclusion, viz.: that anaphylaxis can be produced by the incorporation of non-albuminous substances, as for instance carbohydrates, provided colloids only are concerned, but that the true anaphylactic effect immediately disappears if such solutions are first passed through a Berkefeld filter and the filtrate only is injected, or if the emulsion is considerably heated before injection so that the colloidal solutions are transformed into chemical solutions. They come to the conclusion that in intermittent silver salvarsan treatment the danger of anaphylactoid manifestations comes into question at the time of the first injection, and that for the repeated use of it it would be advisable to commence each fresh series with a small dose in order to first overcome the oversensitiveness.

Angioneurotic Symptoms. Lenzmann states that a strong concentration of silver salvarsan leads to angioneurotic symptoms.

Delbanco and Zimmern⁶ state that patients having a tendency to angioneurotic symptoms should be given injections very slowly.

Schoenfeld and Birnbaum⁸ speak of angioneurotic symptoms which are sometimes followed by collapse.

Kolle¹⁴ states that angioneurotic manifestations are, as a rule, due to the repeated injections of too concentrated doses of the remedy, and in most cases they can be avoided. He further states that in treating patients attention is called to the necessity of good nourishment and to the avoidance of excesses of any kind. By following these directions the angioneurotic symptom-complex can most certainly be avoided. But it should be pointed out that the said symptom-complex does not in any circumstances offer any apprehension, because so far no single case of death due to silver salvarsan has been recorded, in spite of more than 100,000 injections.

Hahn¹⁹ states that the 1-per-cent. solution as used by him renders it possible to prevent the cropping up of angioneurotic symptoms.

Goldberger²⁸ states that he never saw the so-called angioneurotic symptom-complex as described by Pinkus,²⁸ nor the vasomotor signs as were observed by Galewsky²⁸ and Sellei.

The angioneurotic symptoms as described by many authors are: vomiting, dizziness, pain in the back, edema of lips and face.

Spirochetæ Fever. In primary and secondary cases it is no uncommon occurrence to observe a rise of temperature after the first injection, which should be interpreted as spirochetæ fever; this does not constitute a contra-indication against a continuation of the treatment. If there is a higher rise of temperature after the second or third injection, or if the high temperature is continued over a longer period, further treatment must be interrupted for a certain time until the conditions of the patient have resumed their normal state.

Fabry³² states that spirochetæ fever is caused by the decrease in the number of spirochetæ, usually after injections with silver salvarsan in secondary lues. Should salvarsan anaphylaxis set in, increase the interval or decrease the dose.

Our experience has been that we get a reaction after the first dose of any arsenobenzol preparation in late primary or early secondary syphilis. We have always interpreted this as being caused by the spirocheticidal effect of any arsenobenzol preparation on the spirochetæ, thereby suddenly throwing a protein substance in the circulation and producing the so-called spirochetæ fever. This may be interpreted as angioneurotic symptom-complex, or anaphylactoid reaction. We have never seen a reaction following silver salvarsan that we considered alarming.

Neurorelapses. Ehrlich and Gennerich³⁴ have said that mono-recidives are caused by the local spreading of unsterilized spirochetæ. Kolle¹ thinks that we should never be alarmed over neurorelapses, he states there has never been a case of neurorecidive which was later reported as cerebrospinal syphilis. Kreiblich²⁷ and Sellei¹⁸ have not seen cases of nervous relapses after silver salvarsan. Galewsky¹¹ and Sinn³⁵ each report 1 case. In more than 800 cases our records do not show a case of neurorelapse.

Periphlebitis. This rarely occurs and is always due to faulty technic, the extravasation of the solution into the tissues at the site of injection, or trauma to intima of the vein. An abscess at site of injection has occurred only once to my knowledge in our complete series. In the out-patient clinic of this hospital there are given nearly three hundred injections on the morning of the day our out-patients are treated.

Effect on Later Manifestations of Syphilis. Weichbrodt, Knauer, Seoli-Bonn and Gennerich¹⁴ state that the spinal fluid is strongly influenced by silver salvarsan.

Dreyfus⁹ says that silver salvarsan can have after-effects more

frequently than neosalvarsan; however, he reports good results in syphilitic diseases of the nervous system. The best results were obtained in the early stage of the disease. He states that the subjective symptoms disappeared after a few injections and the objective symptoms in one or two weeks.

Kolle¹⁴ speaks of silver having been used for many years in the treatment of nervous diseases with apparently good results.

Hahn¹⁷ states that he obtained good results in cerebral syphilis and remarkable effects in tabes.

Galewsky¹⁵ also obtained good results with silver salvarsan in nervous syphilis.

Goldberger²⁸ is impressed with silver salvarsan and thinks that further investigations should be made with this drug.

In 2 cases in which Friedlaender³⁰ has used silver salvarsan he was led to believe that salvarsan or neosalvarsan is preferable to silver salvarsan in nervous syphilis.

Under the direction of Major Flynn, Captain Kimbrough has obtained the spinal fluid in 19 cases of patients under treatment in this hospital, after having finished their third course of treatment. The laboratory examination was made by Major Gentzkow, who reports the Wassermann negative in all these cases with the exception of 2, in which the spinal fluid gave a plus-minus reaction. The two last-mentioned cases had been treated with other arsenobenzol preparations during the first course of their treatment, and in addition they had not received their treatment regularly. In one of these cases the Wassermann was single-plus strong. The patient did not take treatment regularly, there was a lapse of six months between first and second course, and in the first course the patient was given novo-arsenobenzol rather than silver salvarsan. In the other case the Wassermann was plus-minus and the patient was given novo-arsenobenzol in the first course rather than silver salvarsan.

Captain Price, Chief of the Eye, Ear, Nose and Throat Service, has treated 8 cases of syphilitic iritis which were given silver salvarsan as outlined heretofore in this article. He states that he was greatly impressed with the results obtained by this drug. He wished to emphasize in particular one case which yielded surprisingly rapidly to treatment. The patient in question was almost entirely blind from interstitial keratitis on his admission to the hospital. He further states that the results obtained in this case with seven months' treatment with silver salvarsan were such as ordinarily he could not have expected before seventeen months.

Argyria. We have not been able to find any case of argyria reported in the literature, as the result of silver-salvarsan treatment. Our cases have not developed any such manifestations.

Poison after Administration of Silver Salvarsan. Foulerton³⁶ states it appears that the results characteristic of poisoning by

arsenobenzol compounds may be produced by the action of arsenic alone. But in view of the serious damage to the liver and kidney tissues in experimental poisoning with ortho-amido-phenol it is impossible to ignore the probability that the toxic action of the arsenobenzol drugs may be influenced to some extent by the benzene constituent.

So-called arsenic poisoning from arsenobenzol preparations may be classed as acute, subacute and chronic. In a series of more than 6000 injections of silver salvarsan in patients who are either still under treatment or who have been under treatment with silver salvarsan in conjunction with mercury, there have been only two cases of so-called arsenical poisoning which could be attributed to silver salvarsan. In all the other cases of poisoning at this hospital the patients received novo-arsenobenzol. One of these cases received three doses of silver salvarsan. First dose was fifteen-hundredths (0.15) gm. silver salvarsan, eight-hundredths (0.08) gr. gray oil. Second dose (six days later) two-tenths (0.2) gm. silver salvarsan, eight-hundredths (0.08) gr. gray oil. Third dose (four days later) three-tenths (0.03) gm. silver salvarsan, eight-hundredths (0.08) gr. gray oil. On the same day following the third dose of silver salvarsan and gray oil the patient suffered from headache, chills and dizziness, vomited twice and complained of pain in the epigastric region after the injection of silver salvarsan that day, three days later he developed sore-throat, diffuse erythema over the entire body, face edematous and red, a temperature of 101.4 and slight jaundice. The patient's urine was positive for albumin from the day following the second dose of silver salvarsan until fifteen days later. The other case received the first course of treatment. On the day following the last dose patient states the tips of his fingers and toes felt numb, skin became red in patches, which was quickly followed by a diffuse erythema, urine showed albumin and four days later early evidence of jaundice.

Albuminuria. Müller³⁷ states albumin in the urine was never noticed in his cases. Many authorities consider nephritis as a contra-indication to the administration of salvarsan, even in syphilitic nephritis. Sellei states that silver salvarsan had a favorable influence on the kidney in three cases where there was a nephritis in combination with the syphilis.

About 4 per cent. of our cases show albumin in their urine sometime during their course of treatment. They may be tabulated according to the number of doses of silver salvarsan and mercury as follows:

No. of cases.	No. of doses of silver salvarsan and mercury.	No. of cases.	No. of doses of silver salvarsan and mercury.
1	1	2	6
2	2	8	7
3	3	6	During 2d course.
4	4	3	During 3d course.
7	5		

In about one-half of the cases the albumin cleared up under further treatment and as would be expected these cases were those who showed albumin in the early part of the treatment. On the contrary, in those cases in which the albumin appeared during the latter part of first course or later, there was a tendency for the albumin to persist until further treatment was discontinued.

The confusing factor in cases showing albumin in their urine while under treatment for syphilis is the fact that we may be dealing with a transient or toxic albuminuria, from various causes, *i. e.*, syphilis, mercury, any arsenobenzol preparation or the various organic or infectious diseases.

In view the fact that many writers in using silver salvarsan alone do not speak of an albuminuria, it would indicate that in some of our cases in which this condition presented itself in the latter part of the disease it may have been due to mercury.

It is hoped that a report on albumin occurring during treatment may be made at a later date.

Summary. 1. Silver salvarsan is the strongest spirocheticide as well as being the least toxic of all arsenobenzol preparations, according to results obtained from animal experimentation, that has yet been introduced, and nothing has so far developed in its clinical application to contradict these observations.

2. Silver salvarsan deteriorates rapidly when exposed to the air, and this deterioration is recognized best when the silver salvarsan is placed in solution.

3. Technic of administration requires.

(a) Strict asepsis.

(b) Freshly distilled sterilized water in the proportion of 10 c.c. to each one-tenth (0.1) gm. of silver salvarsan.

(c) Silver salvarsan powder must be completely dissolved before administration.

(d) Proper precaution to prevent extravasation of the silver salvarsan solution into the surrounding tissues is essential.

(e) Slow administration, *i. e.*, not less than one minute.

4. If silver salvarsan is used alone probably the best treatment (based on the results reported in recent literature) is as follows:

Begin the treatment with one-tenth (0.1) gm. of silver salvarsan, increase dosage to two-tenths (0.2) gm. for women and twenty-five-hundredths (0.25) gm. for men as a maximum dose, with an interval of four days between doses, and never give more than 2 gm. in any one month.

5. The results obtained in primary syphilis on the Wassermann reaction are as good, if not better, than with any other arsenobenzol preparation used in combination with mercury.

6. The Wassermann reaction reversed to negative as rapidly in secondary syphilis with mercury and silver salvarsan as in any other arsenobenzol preparation with mercury.

7. Mercury should be given with silver salvarsan in the treatment of syphilis. Whether or not it should be given at the same time or following the silver salvarsan is another question. In military service it is desirable to give the two at the same time.

8. The effect of silver salvarsan on all clinical manifestations of syphilis is decidedly rapid, and appears at least as effective as that of any other arsenobenzol preparation.

9. Alarming effects of silver salvarsan were never seen in any of our cases.

10. Constant vigilance in the administration of all arsenobenzol preparations is essential. Particular attention should be given to patient's weight, a beginning erythema, functional kidney and liver tests.

11. Kolle, Ritz, Galewsky, Hauck and Gennerich appear to be of opinion that silver salvarsan is better than any other salvarsan preparation. Boas, Kissmeyer and Müller seem to think that silver salvarsan is on a par with salvarsan. Dreyfus, Kerl, Schoenfeld, Birnbaum, Bruhns, Lowenberg and Goldberger think that silver salvarsan is better than neosalvarsan. Hoffmann, Knopf, Scholtz and Sinn prefer salvarsan to silver salvarsan. Von Nothhaft says he obtains no better results from silver salvarsan than other salvarsan preparations. Friedlaender, Sellei and Hahn speak of very good results from silver salvarsan; Fabry says it might well be called upon to supplement or supplant neosalvarsan.

Conclusions. 1. Give mercury with silver salvarsan until it has been definitely proved that the mercury is unnecessary.

2. Energetic and intensive silver salvarsan and mercury treatment are indicated in early primary syphilis during the prepositive Wassermann period.

3. Silver salvarsan in so-called abortive treatment of syphilis is not so dangerous as other arsenobenzol preparations.

4. The literature on silver salvarsan and our own experience with this preparation, warrants the further continuation of its use.

5. An excellent field for the further study of these cases and the subject in general is now afforded at the Station and Convalescent Hospitals. It is hoped that the work is just begun, and that by a careful tabulation of the cases now on hand, and the careful observations noted in our syphilitic registers, by the teamwork of the various professional services and with the careful system of follow-up which it is expected to institute, this series of cases alone should in time enable us to draw definite conclusions as to the efficacy of this preparation.

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